

TETRAHEDRON

Total Synthesis of (-)-Halosaline by a Ruthenium-Catalyzed Ring Rearrangement

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Abstract: The stereoselective synthesis of substituted piperidines by a rutheniumcatalyzed ring rearrangement of cyclopentene derivatives is demonstrated. The influence of different substituents and the effect of ethylene on the metathesis reaction is described. The ring rearrangement can be combined with a molybdenum-catalyzed cross metathesis reaction using allyltrimethyl silane as coupling partner. The first total synthesis of (-)-halosaline was accomplished via domino metathesis reaction utilizing Grubbs' ruthenium catalyst. © 1999 Elsevier Science Ltd. All rights reserved.

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Introduction:

During the last several years ring closing metathesis (RCM) has become an important synthetic method particularly due to the development of Grubbs' ruthenium catalyst^[1] 1 $complex^{[2]} 2$ $Cl_2(PCy_3)_2Ru=CHPh (Cy = cyclohexyl)$ molybdenum and Schrock's PhMe₂CCH=Mo=N[2,6-($iPr_2C_6H_3$][OCMe(CF₃)₂]. The efficiency of such ring closure reactions has been demonstrated by the synthesis of numerous carbo- and heterocycles^[3-6]. It has also been applied as key step in several natural product syntheses^[3,7,8]. The formation of a volatile olefin - usually ethylene - is anticipated to be the driving force of the RCM reaction. 1 does also catalyze ring opening metathesis (ROM), which is mainly applied in the ring opening metathesis polymerization (ROMP) of norbornene derivatives^[9,10]. We successfully avoided the polymerization of norbornene derivatives in the presence of a terminal olefin and were able to combine the ROM with a highly selective cross metathesis (CRM)^[11,12]. ROM can also be combined with RCM^[13-15]. The driving force of these reactions is the difference of enthalpy which is mainly due to the loss of ring strain of the reactant cyclic olefin. A particularly attractive aspect of this reaction is the catalytic transfer of stereochemical information from readily available carbocyclic olefins to heterocyclic products.

Here we would like to report the ruthenium-catalyzed ring rearrangement of chiral cyclopentene derivatives and the application of this concept to the synthesis of the piperidine alkaloid (-)-halosaline $3^{[16]}$.



Scheme 1: Ruthenium-catalyzed ring rearrangement.

In a reaction of a cyclopentene derivative A with 1 we expect the terminal double bond to be attacked first to form the metal-carbene complex B (Scheme 1). A reaction of B with A could lead to dimerization products. However, if the intramolecular formation of a metallacyclobutane with the endocyclic double bond followed by [2+2]-cycloreversion was faster, carbene complex C should be obtained. The catalytic cycle could be closed by a reaction of C with another molecule of A. Depending on the regioselectivity of the cycloaddition, a cross metathesis or a methylene transfer, which results in formation of product D, would occur. In case of X = N, O one would transform cyclopentene derivatives into heterocycles, if cross metathesis can be excluded. The A : D ratio should depend on thermodynamic effects, e.g. ring strain. As a side reaction cross metathesis may take place, which is strongly effected by steric parameters. Therefor, the yield should depend on the size of the substituent R.

Results and discussion:

Piperidines are found in many natural products. Consequently, we intended to apply our concept to the stereo-controlled synthesis of this class of compounds. As a target, we chose (-)-halosaline **3** which was isolated from *Haloxylon Salicornicum*^[16]. It is one representative of the group of natural piperidine alkaloids which differs in the relative and absolute configuration at C2 and C8 as well as the length of the alkyl moiety at C8^[17].

Acetate 4 served as starting material. It can be readily prepared in high enantiomeric purity (>99 % ee) by enzymatic hydrolysis^[18] of the meso diacetate and offers a variety of

possibilities for the synthesis of enantiomerically pure diastereomers of type A. The trans cyclopentene derivative 5a was obtained by Mitsunobu reaction^[19] of 4 with *N*-tosyl butenylamine (Scheme 2). A 1:3- mixture of starting material and rearranged product 6a was obtained in the reaction of 5a with 7 mol % of 1, as determined by ¹H-NMR-analysis of the crude product.



Scheme 2: a) 2.5 eq. ADDP, 3 eq. TBP, 2.5 eq. *N*-tosylbutenylamine, benzene. b) NEt_a, MeOH, 18 h. c) TBSCI, imidazole, DMF. d) 7 mol % 1, CH₂Cl₂, rt., 12 h, Cy = cyclohexyl. [e) Ratio of metathesis is given below the arrow.]

Replacing the acetate by a sterically demanding TBS-ether **5b** complete conversion was observed. With 7 mol % 1 after 12 h in CH_2Cl_2 the heterocycle **6b** was obtained in 80% yield after chromatography. By introducing a large substituent on the oxygen the formation of dimerization of products is suppressed. To accelerate the metathesis reaction and to avoid side product formation we investigated the influence of ethylene. Performing the reaction in 0.05-0.1 M concentration of **5b** in CH_2Cl_2 and excess ethylene, an increase in isolated yield up to 97 % was achieved.

The heterocycle **6b** possesses the correct relative configuration at C2 and C8 (2*R*, 8*R*), which is not the absolute configuration of the naturally occurring (-)-halosaline **3** (Scheme 3). For the synthesis of the naturally product the same starting material **4** can be utilized with only a small variation of the reaction sequence. Silylation of the OH-group, hydrolysis of the acetate, and Mitsunobu reaction with the hydroxyl group at C2 gave the (2*S*, 8*S*)-configured product **8** after the metathesis reaction (7 mol % **1**, CH_2Cl_2 , 96 %). Performing the metathesis as an one-pot reaction by adding 3 eq. allyltrimethylsilane, the desired cross metathesis product **9** was only formed with less than 10 % yield and **8** was the main product (react. not shown). We suppose steric effects in the cross metathesis step to be the reason for this low yield. The use of Schrock's much more reactive molybdenum complex **2**, which is known to give higher yields for sterically hindered substrates, only resulted in cross metathesis of the terminal double bond of the cyclopentene derivative **7** with allyltrimethylsilane (react. not shown).



Scheme 3: a) TBSCI, Imidazole, DMF. b) NEt₃, MeOH, 18 h. c) 2.5 eq. ADDP, 3 eq. TBP, 2.5 eq. N -tosylbutenylamine, benzene. d) 5 mol % 1, CH₂Cl₂, rt., 5 h. e) 3 eq. allyltrimethylsilane, 10 mol % 2, CH₂Cl₂.

Therefore we performed the $7 \rightarrow 8$ ring rearrangement using the ruthenium catalyst 1 and utilized the molybdenum complex 2 for subsequent cross metathesis with allyltrimethyl silane. The reaction of the piperidine derivative 8 with allyltrimethylsilane using 2 gave the desired allylsilane 9 in 58 % yield after chromatography (Scheme 3). This product would be suitable for the synthesis of the natural (-)-halosaline 3.



Scheme 4: a) 1.5 eq. dimethylallylchlorosilane, pyridine, CH₂Cl₂. b) 3 eq. DiBAH, THF. c) 2.5 eq. ADDP, 3 eq. TBP, 2.5 eq. *N* -tosylbutenylamine, benzene. d) 5 mol % 1, CH₂Cl₂, rt., 4 h. e) 3 eq. TBAF, -78 °C - warm up, CH₂Cl₂. f) H₂, Pd/C. g) Na/Hg, MeOH, K₂HPO₄, refl. 12 h.

However, to increase the overall yield, we replaced the CRM-step by an additional ring closure metathesis using the cheaper and less sensitive ruthenium catalyst 1 (Sheme 4). Therefore the allyldimethylsilylether was used as protective group in the first synthesis step. A domino metathesis of 10 with 5 % 1 gave the cyclic silyl ether 11 in high yield after 5 h in CH₂Cl₂, as determined by ¹H-NMR. Desilylation was performed without isolation of the metathesis product. Protic conditions resulted in the formation of diene 12. Treatment of 11 with tetrabutylammonium fluoride (TBAF) gave 13 in 78 % yield. 13 was quantitatively hydrogenated using Pd/C under atmospheric pressure. Cleavage of the tosyl-group was achieved using Na/Hg in methanolic phosphate buffer^[20]. (-)-Halosaline 3 was isolated in 82 % yield as a white solid. Spectroscopical data and optical rotation [α]_D = -19.8 (c = 0.6, in 95% EtOH) accorded to the data of the natural product [α]_D = -19.5 (c = 0.6, in 95% EtOH).

With the first total synthesis of (-)-halosaline 3 we demonstrated the high efficiency of the combined ring opening/ring closing metathesis and its potential for the transfer of chirality between different ring systems. This concept of intramolecular ring opening metathesis reaction could serve as a key step in a variety of stereoselective natural product syntheses. The influence of substituents at the cyclic olefin was also demonstrated. Further studies of these effects as well the application of this reaction to other ring systems of different size and constitution are currently investigated and will be reported in due course.

Experimental:

¹H-NMR spectra (400 MHz) and ¹³C-NMR spectra (100.6 MHz) were recorded on a BRUKER AM 400 spectrometer in CDCl₃. NMR chemical shifts are expressed in ppm upfield, relative to the internal solvent peak. Mass spectra were recordet on a FINNIGAN MAT 95 SQ and IR spectra on a NICOLET FT-IR 750 spectrometer. Columm chromatography was performed on MERCK Silica gel 60 (0.040-0.063 mm). Chemicals were purchased from ALDRICH or MERCK and use without further purification. Metathesis reactions were performed in a BRAUN MB 150B-G glove box. Optical rotations were masured on a PERKIN-ELMER 141 polarimeter.

(1S, 4R)-Acetic acid 4-[but-3-envl(toluene-4-sulfonvl)amino]cyclopent-2-envl ester (5a), 4 (100 mg 0.7 mmol), N-tosyl butenylamine (400 mg, 1.76 mmol) and tributylphoshine (TBP) (440 mg, 2.11 mmol) were dissolved in dry benzene (10 mL). Azodicarboxylic dipiperidide (ADDP) (440 mg, 1.76 mmol) was then added in portions over 5 min and the solution was stirred for 24 h. The mixture was concentrated under vacuum and the residue was chromatographed on silica gel using 5 % MTBE/hexane (R_f0.8, 20 % MTBE/hexane) to afford 5a (211 mg, 86 %). IR (film) 3070 (w), 2978 (w), 2931 (w), 2865 (w), 1735 (s), 1641 (w), 1598 (w), 1494 (w), 1370 (m), 1342 (sb), 1238 (sb), 1161 (sb), 1090 (m), 1020 (s), 915, 816, 776, 661 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) $\delta_{\rm H}$ 7.71 (d, J = 8 Hz, 2 H), 7.30 (d, J = 8 Hz, 2 H), 5.86 (dt, J = 6, 2 Hz, 1 H), 5.78 (ddd, J = 6, 2, 1 Hz, 1 H), 5.69 (ddt, J = 17, 10, 7 Hz, 1 H), 5.63 10, 6 Hz, 1 H), 2.71 (ddd, J = 15, 10, 6 Hz, 1 H), 2.44 (s, 3 H), 2.35 (m, 2 H), 2.00 (s, 3 H), 1.94 (ddd, J = 15, 8, 3 Hz, 1 H), 1.86 (ddd, J = 15, 8, 3 Hz, 1 H); 13 C NMR (CDCl₃, 106.4 MHz) δ_c 170.83 (Cq), 143.43 (Cq), 137.17 (CH), 134.70 (CH), 133.47 (CH), 129.78 (CH), 127.17 (CH), 117.01 (CH₂), 78.21 (CH), 63.28 (CH), 43.47 (CH₂), 36.03 (CH₂), 34.58 (CH₂), 21.51 (CH₃), 21.06 (CH₃); HRMS calcd. for [M⁺-Ac] C₁₆H₂₂O₃NS 308.1320, found 308.1319.

(1*R*, 4*S*)-*N*-But-3-enyl-*N*-(4-hydroxycyclopent-2-enyl)-4-methylbenzene sulfonamide. 5a (256 mg, 0.593 mmol) was added to a mixture of NEt₃ (5 mL) and MeOH (5 mL). The solution was stirred for 18 h at room temperature. The solvent was removed under vacuum, the residue was redissolved in two times with MTBE (30 mL) and flushed through silica gel. Removal of the solvent under vacuum gave a clear oil (175 mg, 96 %). IR (film) 3700 - 3200 (b, OH), 3064 (w), 2977 (w), 2943 (w), 1641 (w), 1598 (w), 1494 (w), 1335 (sb), 1158 (s), 1107 (m), 1019 (m), 918, 886, 816, 754 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) $\delta_{\rm H}$ 7.69 (d, J = 8 Hz, 2 H), 7.29 (d, J = 8 Hz, 2 H), 5.85 (dt, J = 6, 2 Hz, 1 H), 5.68 (ddt, J = 17, 10, 7 Hz, 1 H), 5.64 (m, 1 H), 5.24 (m, 1 H), 5.03 (d, J = 17 Hz, 1 H), 5.01 (d, J = 10 Hz, 1 H), 4.85 (m, 1 H), 2.98 (ddd, J = 15, 10, 6 Hz, 1 H), 2.41 (s, 3 H), 2.35 (m, 2 H), 1.95 (sb, OH), 1.82 (ddd, J = 15, 8, 3 Hz, 1 H), 1.69 (ddd, J = 15, 8, 3 Hz, 1 H); ¹³C NMR (CDCl₃, 106.4 MHz) $\delta_{\rm C}$ 143.34 (Cq), 137.48 (CH), 136.90 (Cq), 134.81 (CH), 134.49 (CH), 129.70 (CH), 127.15 (CH), 116.84 (CH₂), 75.68 (CH), 63.54 (CH), 43.40 (CH₂), 37.79 (CH₂), 36.08 (CH₂), (CH), 21.47 (CH₃); HRMS calcd. for [M⁺] C₁₆H₂₁O₃NS 307.1242, found 307.1249.

(1R, 4S)-N-But-3-enyl-N-[4-(tert-butyldimethylsilanyloxy)cyclopent-2-enyl]-4-methyl

benzene sulfonamide (5b). To a solution of (1S, 4S) N-But-3-enyl-N-(4-hydroxycyclopent-2envil-4-methyl benzene sulfonamide (190 mg, 0.618 mmol) and tert butyldimethyl chlorosilane (112 mg, 0.743 mmol) in dry DMF (5 mL) imidazole (50 mg, 0.743 mmol) was added over 10 min. The mixture was stirred for 12 h at room temperature. Hexane (30 mL) and saturated NaHCO₃ solution (10 mL) was added to the solution and the aqueous layer was extracted two times with hexane (20 mL). The combined organic layers were washed with brine (15 mL), dried with MgSO₄ and concentrated to give a clear oil (239 mg, 92 %). IR (film) 3065 (w), 2954 (s), 2874 (s), 2856 (s), 1642 (w), 1599 (w), 1472 (w), 1344 (sb), 1252 (m), 1161 (s), 1091 (w), 1074 (s), 905, 835, 776 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) $\delta_{\rm H}$ 7.71 (d, J = 8 Hz, 2 H), 7.30 (d, J = 8 Hz, 2 H), 5.85 (dt, J = 6, 2 Hz, 1 H), 5.70 (ddt, J = 17, 10, 7 Hz, 1 H), 5.55 (m, 1 H), 5.19 (m, 1 H), 5.04 (d, J = 17 Hz, 1 H), 5.02 (d, J = 10 Hz, 1 H), 4.86 (m, 1 H), 2.98 (ddd, J = 15, 10, 6 Hz, 1 H), 2.68 (ddd, J = 15, 10, 6 Hz, 1 H), 2.43 (s, 3 H), 2.35 (m, 2 H), 1.85 (ddd, J = 15, 8, 3 Hz, 1 H), 1.70 (ddd, J = 15, 8, 3 Hz, 1 H), 0.85 (s, 9 H), 0.02 (s, 6 H); ¹³C NMR (CDCl₃, 106.4 MHz) δ_C 143.20 (Cq), 138.18 (CH), 137.17 (Cq), 134.96 (CH), 133.03 (CH), 129.62 (CH), 127.19 (CH), 116.76 (CH₂), 76.15 (CH), 63.67 (CH), 43.53 (CH₂), 38.39 (CH₂), 36.12 (CH₂), 25.79 (CH), 21.46 (CH₃), 18.12 (Cq), -1.05 (CH₃), -1.10 (CH₃); HRMS calcd. for $[M^+-CH_3] C_{21}H_{32}O_3NSSi 406.1872$, found 406.1878.

(2*R*, 8*R*)-6-[2-(tert-Butyldimethylsilanyloxy)but-3-enyl]-1-(toluene-4-sulfonyl)-1,2,5,6tetrahydropyridine (6b). 5b (250 mg, 0.594 mmol) was dissolved in dry CH₂Cl₂ (10 mL) and C₂H₄ (20 mL) was bubbled slowly through the solution. 1 (35 mg, 0.042 mmol) was added and the mixture was stirred for 12 h. The solvent was removed under vacuum and the residue was chromatographed on silica gel using 10 % MTBE/hexane (R_f 0.65, 20 % MTBE/hexane) to give 6b (243 mg, 97 %). IR (film) 3078 (w), 3033 (w), 2954 (m), 2928 (m), 2856 (m), 1644 (w), 1598 (w), 1494 (w), 1472 (w), 1345 (s), 1331 (m), 1251 (m), 1160 (s), 1097 (s), 948 (s), 837, 778, 710, 691 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) $\delta_{\rm H}$ 7.68 (d, J = 8 Hz, 2 H), 7.23 (d, J = 8 Hz, 2 H), 5.80 (ddd, J = 18, 10, 7 Hz, 1 H), 5.62 (m, 1 H), 5.53 (m, 1 H), 5.18 (d, J = 18 Hz, 1 H), 5.05 (d, J = 10 Hz, 1 H), 4.50 (m, 1 H), 4.31 (dt, J = 7, 7 Hz, 1 H), 3.87 (dd, J = 15, 6 Hz, 1 H), 2.40 (s, 3 H), 1.85 - 1.65 (m, 4 H), 0.92 (s, 9 H), 0.14 (s, 3 H); 0.02 (s, 3 H); ¹³C NMR (CDCl₃, 106.4 MHz) $\delta_{\rm C}$ 142.86 (Cq), 141.49 (CH), 138.55 (Cq), 129.41 (CH), 128.59 (CH), 126.89 (CH), 124.25 (CH), 114.54 (CH₂), 71.68 (CH), 50.88 (CH), 44.03 (CH₂), 38.23 (CH₂), 25.85 (CH₃), 22.81 (CH₂), 21.44 (CH), 18.14 (Cq), -1.02 (CH₃), -1.75 (CH₃); HRMS calcd. for [M⁺-CH₃] C₂₁H₃₂O₃NSSi 406.1872, found 406.1872.

(1*R*, 4*S*)-Acetic acid 4-(tert-butyldimethysilanyloxy)cyclopent-2-enyl ester. This compound was prepared in 97 % yield from 4 by a procedure similar to that employed for the synthesis of 5b. IR (film) 3067 (w), 2955 (s), 2930 (s), 2887 (m), 2858 (s), 1738 (s), 1473 (m), 1368 (s), 1238 (sb), 1105 (m), 1064 (s), 1021 (s), 837, 777 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) $\delta_{\rm H}$ 5.97 (dt, J = 6, 2 Hz, 1 H), 5.88 (m, 1 H), 5.45 (m, 1 H), 4.71 (m, 1 H), 2.80 (ddd, J = 14, 7, 7 Hz, 1 H), 2.04 (s, 3 H), 1.60 (ddd, J = 14, 5, 5 Hz, 1 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ¹³C NMR (CDCl₃, 106.4 MHz) $\delta_{\rm C}$ 170. 90 (Cq), 138.89 (CH), 131.13 (CH), 76.93 (CH), 74.84

(CH), 41.14 (CH₂), 25.85 (CH₃), 21.17 (CH₃), 18.16 (Cq), -1.04 (CH₃), -1.09 (CH₃); HRMS calcd. for $[M^+-H] C_{13}H_{23}O_3Si 255.1416$, found 255.1416.

(1*R*, 4*S*)-4-(tert-Butyldimethysilanyloxy)cyclopent-2-enol. This compound was prepared in 100 % yield from (1*R*, 4*S*)-Acetic acid 4-(tert-butyldimethylsilanyloxy)cyclopent-2-enyl ester by a procedure similar to that employed for the synthesis of **5b**. IR (film) 3700 - 3200 (b, OH), 3061 (w), 2956 (s), 2929 (s), 2885 (m), 2857 (s), 1676 (w), 1472 (m), 1366 (s), 1252 (s), 1128 (m), 1071 (s), 1021 (sb), 905, 836, 776 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) $\delta_{\rm H}$ 5.95 (m, 1 H), 5.89 (m, 1 H), 5.66 (m, 1 H), 5.58 (m, 1 H), 2.69 (ddd, J = 14, 7, 7 Hz, 1 H), 1.74 (b, OH), 1.51 (ddd, J = 14, 5, 5 Hz, 1 H), 0.90 (s, 9 H), 0.09 (s, 6 H); ¹³C NMR (CDCl₃, 106.4 MHz) $\delta_{\rm C}$ 137.00 (CH), 135.57 (CH), 75.21 (CH), 75.07 (CH), 44.70 (CH₂), 25.86 (CH₃), 18.25 (Cq), -1.03 (CH₃); HRMS calcd. for [M⁺-H] C₁₁H₂₁O₂Si 213.1308, found 213.1313.

(1S, 4S)-N-But-3-enyl-N-[4-(tert-butyldimethylsilanyloxy)cyclopent-2-enyl]-4-methyl benzene sulfonamide (7). This compound was prepared in 87 % yield from (1R, 4S)-4-(tertbutyldimethylsilanyloxy) cyclopent-2-enol by a procedure similar to that employed for the synthesis of 5b. Spectroscopical data accorded to the data of 5b.

(2S, 8S)-6-[2-(tert-Butyldimethylsilanyloxy)-but-3-enyl]-1-(toluene-4-sulfonyl)-1,2,5,6tetrahydropyridine (8). This compound was prepared in 96 % yield from 7 by a procedure similar to that employed for the synthesis of 6b. Spectroscopical data accorded to the data of 6b.

(2S, 8S)-6-[2-(tert-Butyldimethylsilanyloxy)-5-trimethylsilanylpent-3-enyl]-1-(toluene-4sulfonyl)-1,2,5,6-tetrahydropyridine (9). 8 (90 mg, 0.214 mmol) and allyltrimethylsilane (37 mg, 0.321 mmol) were dissolved in dry CH₂Cl₂ (1.5 mL). 2 (8 mg, 0.011 mmol) was added and the mixture was refluxed for 12 h. An additional amount of allyltrimethylsilane (37 mg, 0.321 mmol) and 2 (8 mg, 0.011 mmol) was added and the mixture was refluxed for another 12 h. The solvent was removed under vacuum and the residue was chromatographed on silica gel using 10 % MTBE/hexane (R_f 0.6, 20 % MTBE/hexane) to give 9 (63 mg, 58 %, E/Z-ratio: 1.5/1). IR (film) 3030 (w), 2954 (m), 2928 (m), 2856 (m), 1657 (w), 1599 (w), 1495 (w), 1472 (w), 1346 (s), 1331 (m), 1248 (m), 1161 (s), 1094 (m), 1075 (m), 966 (s), 852 (s), 837 (s), 777, 689 cm^{-1} ; ¹H NMR (CDCl₃, 400 MHz) δ_{H} 7.67 (d, J = 8 Hz, 2 H), 7.22 (d, J = 8 Hz, 2 H), 5.56 (m, 3 H), 5.25 (dd, J = 15, 8 Hz, 1 H), 4.37 (m, 1 H), 3.23 (dt, J = 7, 7 Hz, 1 H), 3.87 (dd, J = 15, 6 Hz, 1 H), 3.11 (ddd, J = 15, 12, 5 Hz, 1 H), 2.39 (s, 3 H), 1.9 - 1.60 (m, 4 H), 1.45 (d, J = 8 Hz, 2 H-Z), 1.27 (d, J = 8 Hz, 2 H-E), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.04 (s, 3 H), 0.01 (s, 6 H); 13 C NMR (CDCl₃, 76.6 MHz) δ_{C} 142.77 (Cq), 138.55 (Cq), 131.92 (CH₂), 129.39 (CH₂), 128.57 (CH₂), 127.79 (CH₂), 126.90 (CH₂), 124.21 (CH-E), 122.71 (CH-Z), 71.63 (CH), 51.00 (CH), 44.68 (CH₂), 38.38 (CH₂), 25.98 (CH₃), 23.00 (CH₂-Z), 22.50 (CH₂-E), 21.44 (CH), 18.14 (Cq), -1.81 (CH₃), -3.90 (CH₃) -4.69 (CH₃); HRMS calcd. for $[M^+-CH_3] C_{25}H_{42}O_3NSSi_2$ 492.2423, found 492.2431.

(1*R*, 4*S*)-Acetic acid 4-(allyldimethylsilanyloxy)cyclopent-2-enyl ester. To a solution of 4 (550 mg, 3.87 mmol) and NEt₃ (1.17 g, 11.6 mmol) in dry CH_2Cl_2 (20 mL) allyldimethylchlorosilane (1.3 g, 9.68 mmol) was added over 10 min. The mixture was stirred for 3 h at room temperature. Hexane (20 mL) was added to the solution and the formation of a white solid was observed. The suspension was flushed through silica gel. Removal of solvent under vacuum gave a clear oil (905 mg, 97 %). IR (film) 3077 (w), 2958 (w), 2882 (w), 1737 (s, C=O), 1631 (w), 1368 (s), 1239 (sb), 1102, 1047, 1021, 904, 838 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) $\delta_{\rm H}$ 5.96 (m, 1 H), 5.89 (m, 1 H), 5.87 (ddt, J = 16, 10, 7 Hz, 1 H), 5.44 (m, 1 H), 4.88 (d, J = 16 Hz, 1 H), 4.85 (d, J = 10 Hz, 1 H), 4.70 (m, 1 H), 2.78 (ddd, J = 14, 7, 7 Hz, 1 H), 2.02 (s, 3 H), 1.62 (d J = 7 Hz, 2 H), 1.59 (m, 1 H), 0.13 (s, 6 H); ¹³C NMR (CDCl₃, 106.4 MHz) $\delta_{\rm C}$ 170.77 (Cq), 138.42 (CH), 133.69 (CH), 131.51 (CH), 113.80 (CH₂), 76.8 (CH), 74.60 (CH), 40.80 (CH₂), 24.64 (CH₂), 21.07 (CH₃), -1.99 (CH₃); HRMS calcd. for [M⁺-C₂H₅] C₉H₁₅O₃Si 199.0790, found 199.0794.

(1R, 4S)-4-(Allyldimethylsilanyloxy)cyclopent-2-enol. (1R, 4S)-Acetic acid 4-(allyl dimethylsilanyloxy)cyclopent-2-enyl ester (600 mg, 2.5 mmol) was dissolved in dry THF (30 mL). DiBAH (5 mL, 1.5 M in toluol) was slowly added to the solution and the mixture was stirred for 30 min. For work-up, a saturated Na₂SO₄ solution (2 mL) was added followed by MgSO₄ and a quick filtration through silica gel. Removal of the solvent under vacuum yielded a clear oil (362 mg, 73 %). IR (film) 3700 - 3200 (b, OH), 3077 (w), 3061 (w), 2971 (m), 2959 (m), 2879 (wb), 1631 (m), 1391 (m), 1253 (s), 1127(m), 1070 (s), 1021 (sb), 905, 836 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) $\delta_{\rm H}$ 5.94 (m, 1 H), 5.85 (m, 1 H), 5.78 (ddt, J = 16, 10, 8 Hz, 1 H), 4.87 (d, J = 16 Hz, 1 H), 4.86 (d, J = 10 Hz, 1 H), 4.64 (m, 1 H), 4.56 (m, 1 H), 2.68 (ddd, J = 16, 7, 7 Hz, 1 H), 2.36 (s, OH), 1.63 (d, J = 8 Hz, 2 H), 1.50 (ddd, J = 16, 4, 4 Hz, 1 H), 0.13 (s, 6 H); ¹³C NMR (CDCl₃, 106.4 MHz) δ_c 136.31 (CH), 136.00 (CH), 133.73 (CH), 113.85 (CH₂), 74.95 (CH), 74.90 (CH), 44.30 (CH₂), 24.66 (CH₂), -1.98 (CH₃); HRMS calcd. for [M⁺-H] C₁₀H₁₇O₂Si 197.0998, found 197.0992.

(1*S*, 4*S*)-*N*-[4-(Allyldimethylsilanyloxy)cyclopent-2-enyl]-*N*-but-3-enyl-4-methylbenzene sulfonamide (10). This compound was prepared in 86 % yield from (1*R*, 4*S*)-4-(Allyldimethylsilanyloxy)cyclopent-2-enol by a procedure similar to that employed for the synthesis of 5a. IR (film) 3076 (w), 2956 (m), 2874 (wb), 1641 (s), 1630 (m), 1599 (m), 1451 (w), 1370 (m), 1344 (sb), 1253 (s), 1160 (s), 1091 (s), 1072 (s), 1039 (s), 906, 836, 815 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) $\delta_{\rm H}$ 7.69 (d, J = 8 Hz, 2 H), 7.28 (d, J = 8 Hz, 2 H), 5.84 (m, 1 H), 5.70 (m, 2 H), 5.57 (m, 1 H), 5.18 (m, 1 H), 5.02 (d, J = 17 Hz, 1 H), 5.01 (d, J = 10 Hz, 1 H), 4.85 (d, J = 17 Hz, 1 H), 4.83 (d, J = 10 Hz, 1 H), 2.98 (ddd, J = 14, 10, 6 Hz, 1 H), 2.69 (ddd, J = 14, 7, 4 Hz, 1 H), 1.57 (d, J = 8 Hz, 2 H), 0.03 (s, 6 H); ¹³C NMR (CDCl₃, 106.4 MHz) $\delta_{\rm C}$ 143.18 (Cq), 137.68 (CH), 137.07 (Cq), 136.00 (CH), 133.55 (CH), 129.58 (CH), 127.15 (CH), 116.73 (CH₂), 113.79 (CH₂), 75.89 (CH), 63.57 (CH), 43.49 (CH₂), 38.11 (CH₂), 36.07 (CH₂), 26.87 (CH), 24.59 (CH₂), 21.40 (CH₃), -2.04 (CH₃), -2.06 (CH₃); HRMS calcd. for [M⁺] C₂₁H₃₁O₃NSSi 405.1794, found 405.1796.

(2S, 8S)-1-[1-(Toluene-4-sulfonyl)-1,2,5,6-tetrahydropyridin-2-yl]pent-4-en-2-ol (13). 10 (280 mg, 0.691 mmol) and 1 (29 mg, 0.035 mmol) were dissolved in dry CH₂Cl₂ (10 mL) and stirred for 5 h. The solution was then cooled to -78 °C and dry tetrabutylammonium fluoride solution (2.1 mL, 1 M in THF) was added. The reaction mixture was allowed to warm to room temperature while stirring for 15 min. The solvent was removed under vacuum and the residue was chromatographed on silica gel using 10 % MTBE/hexane (Rf 0.3, 50 % MTBE/hexane) to give 13 (172 mg, 78 %) and 21 mg 12 (10 %). 13: IR (film) 3700 - 3200 (b, OH), 3071 (w), 3031 (w), 2976 (w), 2928 (wb), 2849 (w), 1640 (w), 1598 (w), 1494 (w), 1380 (m), 1341 (s), 1326 (s), 1156 (s), 1099 (s), 917 (s), 815, 712, 691 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) $\delta_{\rm H}$ 7.68 (d, J = 8 Hz, 2 H), 7.23 (d, J = 8 Hz, 2 H), 5.88 (ddt, J = 17, 10, 7 Hz, 1 H), 5.51 (s, 2 H), 5.09(db, J = 17 Hz, 1 H), 5.05 (db, J = 10 Hz, 1 H), 4.50 (dd, J = 12, 3 Hz, 1 H), 3.98 (m, 1 H), 3.89(ddd, J = 15, 4, 4 Hz, 1 H), 3.52 (OH), 3.08 (ddd, J = 15, 7, 7 Hz, 1 H), 2.39 (s, 3 H), 2.26 (m, 2 H), 1.70 - 1.55 (m, 4 H); ¹³C NMR (CDCl₃, 106.4 MHz) δ_C 143.37 (Cq), 137.85 (Cq), 135.15 (CH), 129.60 (CH), 128.00 (CH), 126.81 (CH), 126.76 (CH), 124.72 (CH), 116.92 (CH₂), 66.18 (CH), 66.13 (CH), 63.09 (CH), 50.72 (CH), 50.61 (CH), 41.10 (CH₂), 40.87 (CH₃), 37.99 (CH₂), 22.23 (CH₂), 22.13 (CH₂), 21.46 (CH₃); HRMS calcd. for [M⁺] C₁₇H₂₃O₃NS 321.1399, found 321.1389; Anal. calcd. for C₁₇H₂₃O₃NS: C, 63.52; H, 7.21; N, 4.36. Found: C, 62.98; H, 7.31; N, 4.33.

12: IR (film) 3518 (wb), 3083 (w), 3064 (w), 3034 (w), 2927 (w), 2854 (w), 1923 (w), 1806 (w), 1727 (w), 1690 (w), 1653(w), 1598 (w), 1495 (w), 1455(w), 1433 (w), 1378 (m), 1342 (s), 1330 (s), 1159 (s), 1097 (s), 1005 (m), 953 (s), 815 713, 688 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) $\delta_{\rm H}$ 7.69 (d, J = 8 Hz, 2 H), 7.29 (d, J = 8 Hz, 2 H), 6.27 (ddd, J = 17, 10, 10 Hz, 1 H), 6.03 (dd, J = 15, 10 Hz, 1 H), 5.65 (m, 3 H), 5.09 (d, J = 17 Hz, 1 H), 5.00 (d, J = 10 Hz, 1 H), 4.35 (m, 1 H), 3.82 (dd, J = 15, 7 Hz, 1 H), 3.11 (ddd, J = 17, 13, 5 Hz, 1 H), 2.40 (s, 3 H), 1.90 (m, 1 H), 1.77 (ddd, J = 19, 5, 5 Hz, 1 H); ¹³C NMR (CDCl₃, 106.4 MHz) $\delta_{\rm C}$ 142.97 (Cq), 138.53 (Cq), 136.81 (CH), 133.79 (CH), 129.93 (CH), 129.52 (CH), 127.39 (CH), 126.99 (CH), 125.47 (CH), 115.89 (CH₂), 53.34 (CH), 38.63 (CH₂), 23.27 (CH₂), 21.45 (CH₃); HRMS calcd. for [M⁺] C₁₇H₂₁O₂NS 303.1293, found 303.1296.

(2*R*, 8*S*)-1-[1-(Toluene-4-sulfonyl)piperidin-2-yl]pentan-2-ol. 30 mg of Pd/C (10 %) was added to a solution of 13 (170 mg, 0.53 mmol) in MTBE (20 mL) under H₂-atmosphere. The suspension was stirred for 8 h. The catalyst was filtered off and the solvent was removed under vacuum to give white solid (170 mg, 99 %,). IR (film) 3700 - 3200 (b, OH), 2936 (s), 2870 (m), 2746 (w), 1598 (w), 1495 (w), 1330 (s), 1304 (m), 1155 (s), 1143 (s), 931 (s), 815, 714, 698 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) $\delta_{\rm H}$ 7.72 (d, J = 8 Hz, 2 H), 7.27 (d, J = 8 Hz, 2 H), 4.20 (m, 1 H), 3.88 (ddd, J = 15, 4, 4 Hz, 1 H), 3.74 (m, 1 H), 3.42 (OH), 2.97 (ddd, J = 15, 14, 3 Hz, 1 H), 2.39 (s, 3 H), 1.98 (ddd, J = 15, 14, 2 Hz, 1 H), 1.55 - 0.95 (m, 11 H), 0.90 (t, J = 7 Hz, 3 H); ¹³C NMR (CDCl₃, 106.4 MHz) $\delta_{\rm C}$ 143.06 (Cq), 137.57 (Cq), 129.73 (CH), 126.59 (CH), 66.66 (CH), 49.44 (CH), 40.72 (CH₂), 38.96 (CH₂), 37.46 (CH₂), 27.67 (CH₂), 23.76 (CH₂), 21.40 (CH₃), 19.07 (CH₂), 18.55 (CH₂), 14.09 (CH₃); HRMS calcd. for [M⁺] C₁₇H₂₇O₃NS 325.1712, found 325.1717. Anal. calcd. for C₁₇H₂₇O₃NS: C, 62.74; H, 8.36; N, 4.30. Found: C, 62.54; H, 8.32; N, 4.43.

(2*R*, 8*S*)-1-Piperidin-2-yl-pentan-2-ol (-)-halosaline (3). (2*R*, 8*R*) 1-[1-(Toluene-4-sulfonyl) piperidin-2-yl]pentan-2-ol (100 mg, 0.31 mmol) and K₂HPO₄·3H₂O (425 mg, 1.86 mmol) dissolved in dry MeOH (7 mL). Na/Hg (5.87 g, freshly prepared from 170 mg of Na and 5.7 g of Hg) was added and the mixture was refluxed for 12 h. 25 mL of H₂O was then added and the aqueous layer was extracted four times with 30 mL of CH₂Cl₂. The combined organic layers were dried with MgSO₄ and concentrated. The residue was chromatographed on silica gel (R_f 0.35, 30 % MeOH/CH₂Cl₂ 5 % NH₃·H₂O) to give 42 mg (82 %) (-)-halosaline 3. [α]_D = -19.8 (c = 0.6, in 95% EtOH); IR (film) 3700 - 3200 (b, OH), 2954 (s), 2929 (s), 2856 (m), 1568 (w), 1452 (m), 1330 (m), 1070 (m), 1053 (m), 1027 (m), 935 (w), 886, 780, 742 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ_H 3.88 (m, 1 H), 3.45 (NH, OH), 3.05 (dd, J = 12, 3 Hz, 1 H), 2.88 (m, 1 H), 2.56 (ddt, J = 14, 12, 3 Hz, 1 H), 1.98 (m, 1 H), 1.65 - 1.25 (m, 11 H), 0.91 (t, J = 7 Hz, 3 H); ¹³C NMR (CDCl₃, 106.4 MHz) δ_C 68.62 (CH), 54.77 (CH), 46.77 (CH₂), 41.83 (CH₂), 31.23 (CH₂), 25.84 (CH₂), 24.59 (CH₂), 18.99 (CH₂), 14.15 (CH₃); HRMS calcd. for [M⁺] C₁₀H₂₁ON 171.1623, found 171.1642. Anal. calcd. for C₁₀H₂₁ON: C, 70.12; H, 12.36; N, 8.18. Found: C, 68.22; H, 12.10; N, 7.74.

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